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VEGETABLE OILS IN NUTRITION

with special reference to
unsaturated fatty acids

VEGETABLE OILS IN NUTRITION

with special reference to unsaturated fatty acids

by

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Printed in the United States of America
Second Printing 462-1-57

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Preface

Within the past three decades has come the realization that fats and oils are not merely sources of calories, but also have certain vital functions which cannot be performed by other classes of foodstuffs. Differences in the compositions of fats and oils, therefore, must be considered seriously in the planning of well-balanced, appetizing meals. Interest in atherosclerosis and heart disease are further drawing unprecedented attention to the roles of fatty foods in human nutrition.

Experimental studies, largely conducted on animals, have shown that certain unsaturated fatty acids are essential for growth, pregnancy and lactation, and the maintenance of normal skin, liver and kidney functions. These same fatty acids are involved in the transport and utilization of cholesterol and thus influence the blood level and state of dispersion of this sterol which is so intimately associated with atherosclerosis. The feeding of large amounts of hydrogenated fats, exposure to x-irradiation, and other stress conditions have been shown to increase the requirements for the essential fatty acids and to aggravate marginal deficiencies in animals.

Fat deficiency in acute form has seldom been observed in

human beings, but there are indications that chronic disturbances in lipid metabolism may be widespread. In consequence, many authorities believe that both the composition and the quantity of fats in human diets must be given careful consideration. Because vegetable oils contain more of the nutritionally essential unsaturated fatty acids than do animal fats or hydrogenated shortenings, certain authorities now believe that the consumption of vegetable oils should be increased at the expense of other types of fats.

This viewpoint has such important implications that many research workers are intensively studying the functions and metabolism of the various fatty compounds. This monograph is offered as a brief review of the ever-growing literature on this vital topic. We hope you will find it useful and invite your comments.

DOROTHY M. RATHMANN, PH.D.

Pittsburgh, Pa.
January 8, 1957

I

Roles of Dietary Fat

MODERN RESEARCH is proving what cavemen knew instinctively: fats and oils are highly desirable foodstuffs. They contribute materially to the appetite appeal and satiety value of the diet. They provide high energy in low bulk, carry fat-soluble vitamins and aid in the utilization of other classes of foodstuffs. Most important, they provide building blocks for structural components in the cells of all tissues and are essential parts of vital organs. In man and most animals, the ability to synthesize certain of these building blocks, the unsaturated essential fatty acids, is so limited that these must be obtained almost entirely from fatty foods.

Fat-free diets such as the Kempner rice and fruit diet[134] are monotonous and unpalatable, and so are tolerable only under unusual circumstances. Although pure fats are virtually tasteless and odorless they readily absorb and enhance flavors, and thus modify the taste and aroma of foods to an important degree. Just the terms, fried chicken, bacon and eggs, steak, or strawberry shortcake conjure up visions of gastronomic delights unattainable on a fat-free diet.

Whether the human craving for fat is psychological or an

instinctive response to a fundamental physical need is impossible to decide on the basis of current evidence. Certainly, individual intakes vary widely. Habit, availability and economic factors all play a part in determining the amount and kind of fat which is eaten.

Highly important from a nutritional point of view is the value of fats *per se* as a concentrated source of energy. Whereas dry proteins and carbohydrates yield 4.1 calories per gram, fats yield more than twice as much energy, that is, 9.3 calories.[65] For this reason, when bulk in the diet must be restricted, a high fat intake may be desirable. This can be achieved in some cases merely by eating fat-rich foods, and in others by the administration of vegetable oil emulsions, either orally[9,105,151,167] or parenterally.[94,100,214,230,231,233]

Given a free choice, humans prefer diets in which fats supply 20 to 40 per cent of the calories. For example, as economic conditions have improved in the United States, the average consumption of fat has increased from 32 per cent of the total calories in 1909 to 40 per cent in 1952.[88] There remain many questions about why this level of fat is desirable. Undoubtedly, some of the answers involve palatability of the food, the efficiency of its utilization, the protein-sparing action of fat, the absorption of fat-soluble vitamins, and the individual's capacity to do work.

Experimental studies have shown this level of fat to be optimal for the growth of young animals.[64,65,74] The superior growth on diets containing 30 per cent of the calories as fat, as compared to 5 per cent, was observed even when rats were given isocaloric amounts of the two diets and, thus, was not due to differences in caloric intake. This growth effect may have been due to the greater quantity of essential fatty acids in the high-fat diet. An equally important factor may have been the

"associative dynamic action" of the fat.[65,89,90] In other words, less heat is lost from the body during the period of digestion, absorption and transport following a high-fat meal than after a low-fat meal. This greater efficiency in food utilization can cause a more rapid rate of growth.

Carbohydrates are generally known to have a protein-sparing action, and a similar effect of fats can be demonstrated under certain conditions. The excretion of nitrogen by human patients maintained on protein-free diets was significantly reduced by addition of fat to the diet.[200] The excretion of amino acids by rats was less on a diet containing 8 per cent corn oil than on a fat-free diet.[174] Ingestion of cottonseed oil also reduced the catabolism of tissue protein in rats fed limited amounts of a protein-free ration.[92]

Following maintenance for one month on a diet in which fats supplied 80 per cent of the calories, rats survived longer, had a greater capacity to do work, and excreted less nitrogen during a prolonged fast than they did after one month on a high-protein or high-carbohydrate diet.[192] While experimental data are not entirely conclusive, they indicate that fat was readily utilized for muscular work in the dog, and that fasting rats were able to work for a longer time when the previous diet contained ample amounts of fat than when it was fat-free.[65]

There is general agreement that dietary fat promotes the absorption of vitamins A, D, E and K.[63,65] Absorption is reduced in the absence of dietary fat or in the presence of large amounts of saturated, high-melting fats. Under such conditions deficiencies may develop even though otherwise adequate quantities of these vitamins are consumed.

One other important effect may be as much psychological as physiological but is no less real. This is the feeling of well-being

and satiety that follows the eating of fatty foods. During World War I there were complaints from Welsh miners that their food did not enable them to work normal shifts. One explanation[58] was that, "they were used to taking with them to their work pies made of fat pastry with a little meat, and it was impossible to make the pastry in consequence of the absence of fat." Similar experiences have been common whenever and wherever fat shortages develop. Perhaps the reason lies in the rate of digestion of fats. Because they are digested more slowly, absorption is also slower than in the case of proteins and carbohydrates. Thus hunger may be appeased for a longer time. This satiating effect of fats has been used to good advantage in the formulation of several reducing diets.[9,96]

II

Nature of Fats

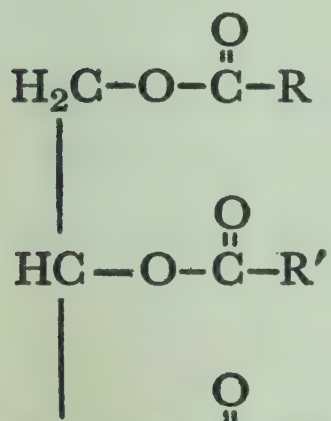
UNTIL QUITE RECENTLY, dietary fats were considered to be only particularly rich sources of energy without any unique metabolic functions. It is becoming increasingly apparent, however, that the quality as well as the quantity of the dietary fat is an important factor in establishing optimum nutrition.

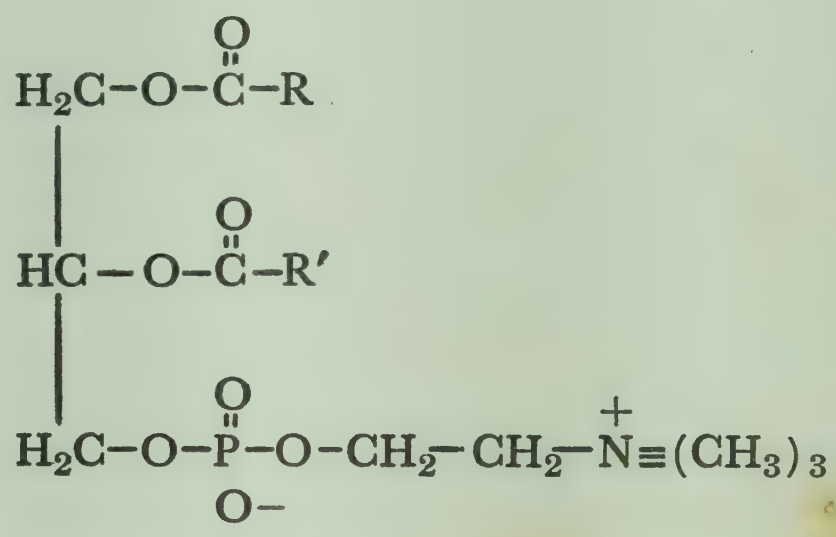
We speak casually about fats and oils in the diet often without stopping to think about the types of compounds involved and what effects each may have. Even the terminology can become confusing, because the word "fat" has two different meanings. It may be used as the inclusive term for all kinds of fatty substances or it may designate only glyceride mixtures which are solids at room temperature. By the latter convention, "oils" are liquid glyceride mixtures. In general, hydrogenated shortenings and animal fats are solids whereas vegetable oils are liquid.

For the purposes of the present discussion, *fat* will be used as the inclusive term when no distinction seems necessary. "Animal fat," "vegetable oil," etc., will be used when the nature of the source has an important bearing on the interpretation of experimental results.

Lipid is another term which is frequently used to designate fatty substances. As a class, the lipids include triglycerides and numerous more complex compounds such as phosphatides (or phospholipids) and sterol esters.

The major components of all fats, vegetable or animal, are *triglycerides* (I), that is, the glycerol esters of *fatty acids*. As a general rule, the naturally occurring fatty acids have an even number of carbon atoms in a straight chain; the vast majority belong to the C_{16} and C_{18} series and may be saturated, or contain one or more double bonds.





Wherein *R* is the hydrocarbon portion of a fatty acid.

I II

Phosphatides (II) are similar to triglycerides in being the fatty acid esters of glycerol. They are more complex, however, since their molecules also contain phosphate groups, various amino compounds and sometimes alcohols other than glycerol. Since phosphatides, such as *lecithin* (II), are natural emulsifiers, one of their primary functions may be to aid in the dispersal and transport of the water-insoluble fatty compounds within the body.

The characteristics of a particular fat are determined to a considerable extent by the relative proportions of the different fatty acids built into the glyceride molecules. For example, coconut oil is liquid because of the high proportion of lauric and other relatively *short-chain saturated acids*. On the other hand, corn oil is liquid because its glycerides contain primarily the *di-unsaturated linoleic acid* (III) and the *mono-unsaturated oleic acid* (IV). Beef tallow is solid because it consists chiefly of glycerides of the relatively *long-chain saturated palmitic* and *stearic* (V) *acids*. Hydrogenated shortenings are solids because they have been prepared by the saturation of many of the double bonds in cottonseed or soybean oil.

$$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$$

III

$$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$$

IV

$$CH_3(CH_2)_{16}COOH$$

V

The compositions and properties of common animal and vegetable fats are summarized in Tables I-A and I-B.

Although the glycerides are the major components, certain minor constituents have an important bearing on the physiological behavior of fats. These constituents are the phosphatides, sterols, vitamins, pigments and antioxidants.

All sterols are solid alcohols which often occur as fatty acid esters. In spite of the fact that sterols and their esters are almost completely insoluble in water, they are readily carried in tissue

TABLE I-A

COMPARATIVE COMPOSITIONS OF FATS*

FAT	FATTY ACIDS AS PERCENTAGE OF TOTAL ACIDS[a]								
	SATURATED		OLEIC		LINOLEIC		LINOLENIC		ARACHIDONIC
	AVE.	RANGE	AVE.	RANGE	AVE.	RANGE	AVE.	RANGE	AVE.
Butter	—	46-48	—	—	4.0[b]	—	1.2[b]	—	0.2[b]
Coconut oil	—	75-88	—	5-8	—	1.0-2.5	—	—	—
Corn oil	13	11-15	—	23-40	56	46-66	—	0.0-0.6[c]	—
Cottonseed oil	26	21-30	27	22-36	47	34-57	—	—	—
Lard	43	—	46	—	10	15.6[b]	0.5	—	0.5 (2.1[b])
Linseed oil	—	6-12	—	13-31	—	10-27	—	30-64	—
Margarine	23	15-23	62	59-77	5.8[d]	5-11	—	0.1-0.9	0
Olive oil	—	8-16	—	53-86	—	4-20	—	—	—
Peanut oil	17	14-22	54	44-65	29	20-37	—	—	—
Shortening	25	17-45	62	43-79	5	3-12	—	0.2-0.6	0-0.5
Soybean oil	15	11-18	25	18-58	55	28-62	5.1	0.3-10	—
Tallow (beef)	53	—	42	—	4	5.3[b]	0.5	—	0.5

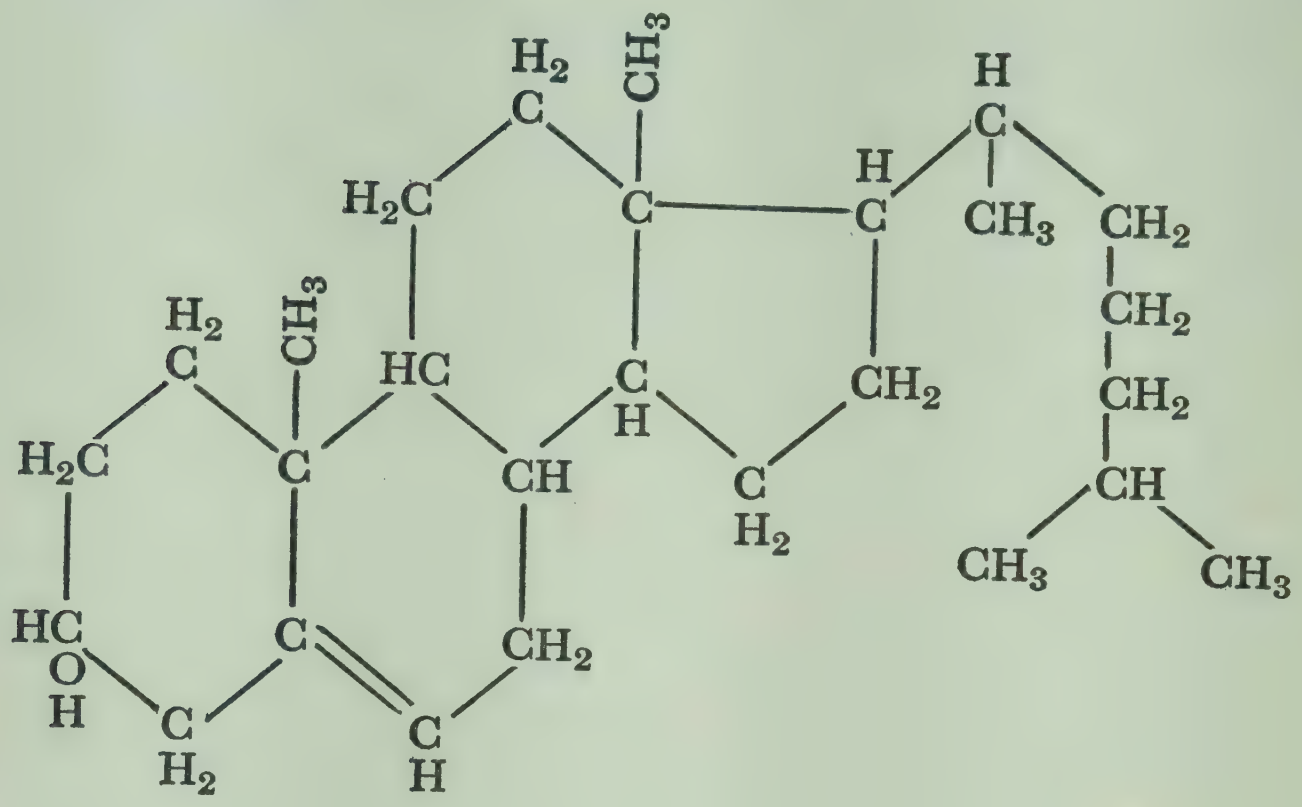
TABLE I-B

COMPARATIVE PROPERTIES OF FATS*

FAT	MELTING POINT (°C) AVERAGE	MELTING POINT (°C) RANGE	IODINE VALUE AVERAGE	IODINE VALUE RANGE	UNSAPONIFIABLE MATTER %, MAX	REFERENCES[a]
Butter	—	28-35	—	26-42	—	15, 65
Coconut oil	—	23-26	—	7-10	0.5	15, 75, 124, 223a
Corn oil	—	—	126	113-131	2	15, 211
Cottonseed oil	—	—	105	90-117	1.5	15, 213, 223a, 228
Lard	38	33-46	—	53-77	0.8	14, 15, 65
Linseed oil	—	—	—	170-204	1.7	15, 75, 124, 223a
Margarine	—	—	81	74-85	—	65, 69, 160, 212
Olive oil	—	—	—	80-88	1.8	15, 75, 124
Peanut oil	—	—	98	90-102	1	15, 91, 223a
Shortening	—	—	78	59-80	—	65, 69, 160, 212
Soybean oil	—	—	130	100-143	1.5	15, 197, 223a, 229
Tallow (beef)	44	40-48	—	40-48	1	14, 15, 65

*These values are typical for products available in the United States. Individual samples or products available in other countries may have values outside the ranges given here because compositions are greatly affected by genetic factors, growing conditions, and processing methods.

a. References and footnotes given in Table I-B also apply to Table I-A.
b. Maximum content.
c. The occurrence of any linolenic acid is doubtful; value reported may be caused by an artifact.
d. As determined by bioassay.



VI

fluids as combinations with proteins, and/or phosphatides. The characteristic sterol of animal fats is *cholesterol* (VI). Vegetable oils frequently contain mixtures of very similar compounds known as *sitosterols*.

Since glycerides have a high energy value and are insoluble in water, they are ideal storage materials. Thus, they are deposited in large amounts in adipose tissue whenever the caloric intake exceeds energy expenditures. Phosphatides and sterols, however, are essential constituents of most cells and probably have specific functional activities. Each tissue seems to have a characteristic phosphatide-to-cholesterol ratio[32,63] which remains constant during the normal fat storage and mobilization processes. However, values outside the usual range are found in many pathological conditions.

III

Effects of Diet on Tissue Lipid Compositions

FATS AND OTHER LIPIDS in the animal body are derived from two sources: (a) they may be built up from the products formed during the digestion and absorption of dietary fats or (b) they may be synthesized from the small molecules produced during the metabolism of all classes of foodstuffs.

The digestibility of most dietary fats is high, usually over 95 per cent. The digestibility is, however, related to the melting point, as is evident from the fact that fats which melt appreciably above body temperature are poorly absorbed.[46,63,65] Metabolic studies have demonstrated repeatedly that vegetable oils are well digested, even by infants and young children,[128,188,224] and have completely refuted the old prejudices concerning fat indigestibility.

During the processes of digestion and absorption the dietary lipids are, to a considerable extent, broken down into their constituent parts. Since both dietary and tissue lipids are made of the same building blocks, the utilization of these parts from the food is not surprising. Dietary fatty acids, for example, are readily incorporated into tissue lipids in quantities regulated by the energy requirements and other needs of the body.

As all types of foods, carbohydrates and proteins as well as fats, are metabolized, numerous small molecules are formed. From these fragments, many of the complex components of tissue cells are synthesized. Thus, for example, cholesterol, the saturated fatty acids, and oleic acid can be synthesized as needed, in apparently unlimited amounts, and are readily built into more complex lipids. But *synthesis of linoleic acid,* either from small fragments or by the introduction of a second double bond into the oleic acid molecule, *seems to be extremely limited.*[23,65,165]

Low-Fat Diets

Because the capacity to synthesize linoleic and the more highly unsaturated fatty acids is limited, relatively hard fats are deposited in the adipose tissues of animals maintained on fat-poor, carbohydrate-rich diets. These fats (Table II) contain an unusually high proportion of saturated and a low proportion of unsaturated fatty acids.[32,40,63,155,156]

Low-fat diets are frequently advocated for reducing the caloric intake in obese patients or for lowering serum cholesterol levels in atherosclerotic individuals. Repeated observations in humans[125,134,136,162,215,234,243] have shown that low-fat diets do indeed cause blood cholesterol levels to fall under certain circumstances, especially in cases of hypercholesterolemia. However, when similar reductions in blood cholesterol levels were achieved in rats on fat-deficient diets, there were also such undesirable concurrent effects as the development of fatty livers caused by cholesterol deposition,[11] or increased requirements for thiamine and pyridoxine[65] and possibly other vitamins.

TABLE II

EFFECT OF DIET ON DEPOT FAT COMPOSITION*

ANIMAL	DIET	SATURATED ACIDS	OLEIC ACID	LINOLEIC ACID
Rat	Low-fat, high-carbohydrate	30.2	47.2	2.2
	5% fat	30.6	44.3	18.6
	High corn oil	15.8	44.8	32.3
	High coconut oil	68.4	23.8	1.4
Hog	Low-fat	40.9	50.2	8.9
	+ 4% cottonseed oil	47.2	39.5	13.3
	+8% cottonseed oil	41.4	31.8	26.8

*Selected from data compiled by Deuel.[62]

Normal and High-Fat Diets

During postprandial absorption, lipid levels in the blood and lymph rise and the plasma becomes milky due to its increased fat content (chylomicronemia). After a high-fat meal, the plasma lipid level reaches a maximum at 5 to 6 hours and returns to normal within 9 to 10 hours[63] as a result of utilization and storage in the tissues. Chylomicronemia is reported to be more intense in men with coronary artery disease[19a] and in older individuals where it persists longer than in young persons.[21,97]

Lipids are withdrawn from the circulation by the cells and used for energy or the synthesis of tissue lipids. In the adipose tissues, regulatory mechanisms control the proportions of saturated and unsaturated fatty acids so that the melting point of the storage fat is maintained within the best range for easy utilization.[32,63] However, as the data in Table II show, the composition of adipose fat may be significantly affected by changes in the characteristics of the dietary fats.

Such is not necessarily the case with the tissue phosphatides and cholesterol esters. These two classes of lipids are active metabolic intermediates and essential structural elements of the cells. Alterations in their compositions may be associated with pathological changes in vital organs, such as have been observed, for example, in experimental animals when dietary supplies of the essential fatty acids have been limited. The possibility that cholesterol metabolism is, to a substantial degree, under the influence of essential fatty acids has led to a hope that the clinical course of atherosclerosis may be favorably influenced by increasing the consumption of vegetable oils in preference to solid fats.

Effects of Diet on Tissue Lipid Compositions

Effect on Blood Cholesterol Levels

A major dissimilarity between vegetable oils and animal fats is the result of differences in the constituent sterols. In humans, the cholesterol which occurs in animal fats is readily absorbed but the sitosterols occurring in vegetable oils are only slightly absorbed. This finding has led to such extreme suggestions as that all animal fats must be eliminated from the diet if human beings are to avoid hypercholesterolemia and atherosclerosis. The validity of such conclusions is questionable, however, in view of the facts that cholesterol is readily synthesized by many tissues,[63] and that it is formed from the numerous small molecules which are normal metabolites of carbohydrates and proteins as well as fat. In addition, the rate of synthesis, at least in the liver, is influenced by the amounts of cholesterol ingested and excreted.[12,59,93,222,223] The operation of such regulatory mechanisms may be one explanation for the lack of a correlation between cholesterol intake and human serum cholesterol levels.[137] Furthermore, the fecal excretion of cholesterol is affected by the nature of dietary fats,[47,138,154] for example corn oil has been found to increase cholesterol elimination whereas beef tallow actually decreased it slightly. It has also been reported that the activity of hypocholesteremic fractions from brain is greater when corn oil rather than cottonseed oil is the carrier.[132a]

Because sitosterols are only slightly absorbed, they may interfere with the absorption of cholesterol and thereby cause significant reductions in serum cholesterol levels.[17,25,26,83,133,153,177,202] For this reason, the ingestion of sitosterol preparations has been recommended as a therapeutic means for reducing and controlling hypercholesterolemia.[24a,189a] When uniformly distributed in a formula diet, β-sitosterol has been observed to

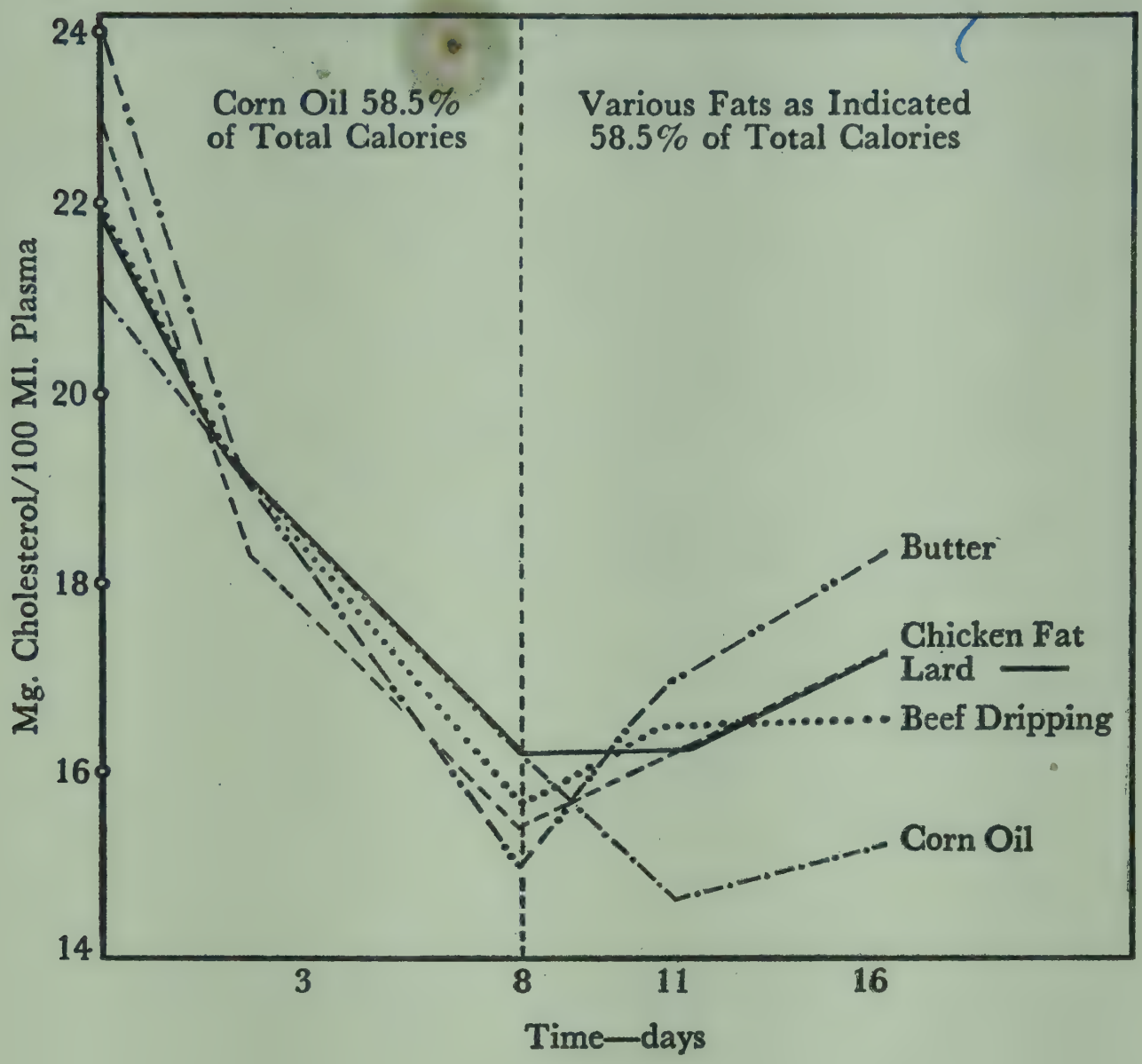
produce a lowering in plasma cholesterol levels even when butter supplied 60 per cent of the calories.[27a]

Clinical studies have repeatedly demonstrated direct correlations between blood cholesterol levels and both the nature and quantity of dietary fats. In 1955 Beveridge *et al.*[28] described changes in plasma cholesterol and phosphatide levels which occurred when five male subjects were transferred from free choice diets to experimental diets in which the nature and amount of fat were controlled. Results of this study and a previous one[162] demonstrated that a statistically significant lowering of the serum cholesterol levels occurred during the ingestion of a diet rich in corn oil as contrasted to similar diets containing butter in equivalent or smaller amounts.

In a more extensive study wherein the nature of the dietary fat was varied systematically, Beveridge *et al.*[27] obtained the results shown in Figures 1, 2 and 3. These authors then stated that, "These observations permit the conclusions that (1) corn oil contains a factor [or factors] that leads to a depression of plasma cholesterol levels and (2) all fats of animal origin so far tested, beef drippings, chicken fat, lard, and butter, contain varying amounts of a factor [or factors] that effects an increase in plasma cholesterol levels." No appreciable concentration of the active factors was achieved by molecular distillation[27a] since considerable activity was found in the first fraction and the fourth fraction which, in the case of corn oil, consist respectively primarily of unsaponifiable matter and almost pure triglycerides.[184a]

Ahrens and co-workers[10] observed comparable changes when patients were fed liquid diets consisting of fat, protein and carbohydrates in caloric proportions of 40-15-45 per cent respectively. These diets were adequate to maintain constant body weights throughout the 20 to 50 week experimental

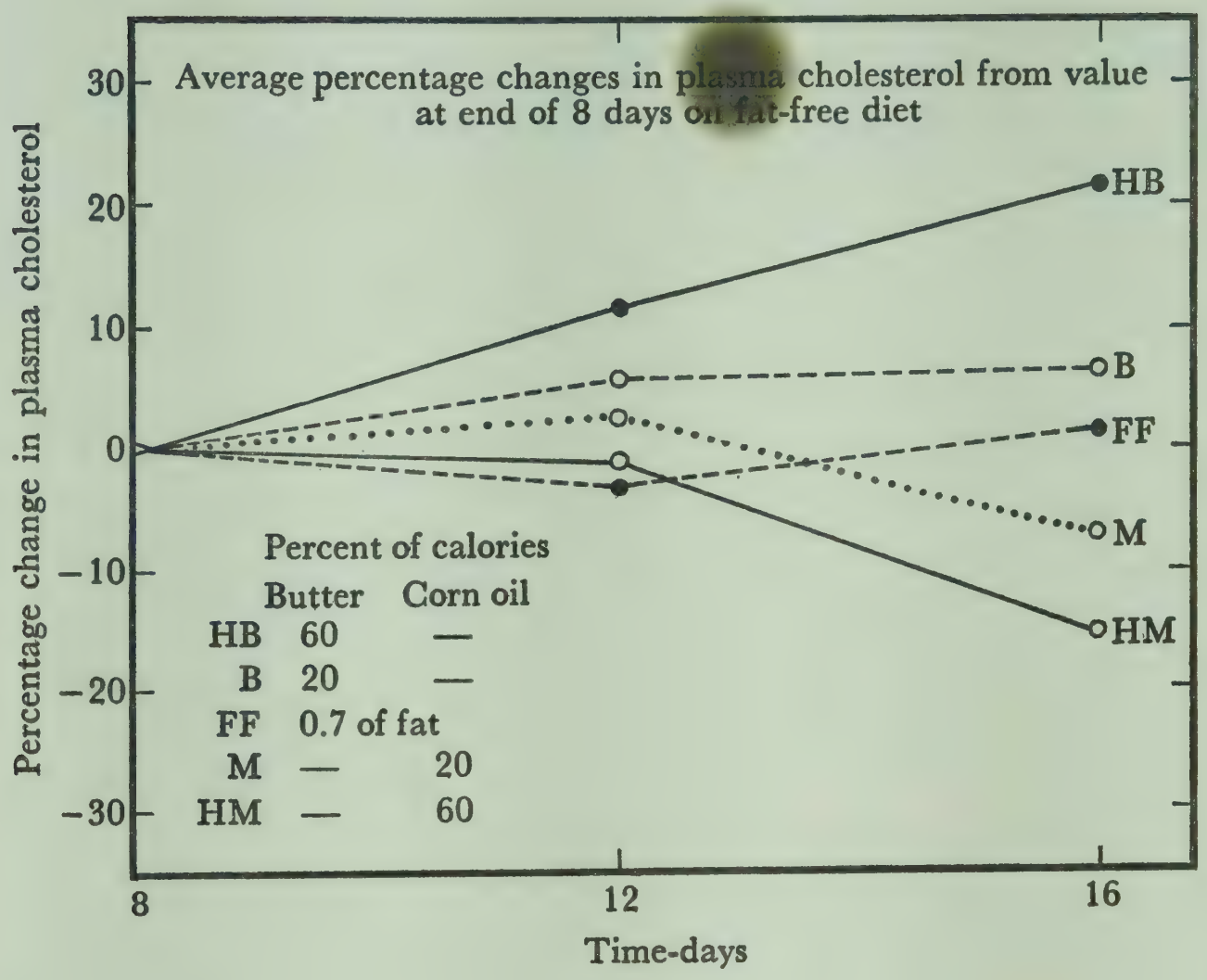
FIGURE 1



Average values for plasma total cholesterol of 30 subjects during a period of eight days on a homogeneous formula diet in which corn oil supplied 58.5% of the total calories and during a subsequent similar period in which the subjects were divided into five groups and consumed diets differing only in the nature of the fat moiety.

Data reported by Beveridge *et al.*[27] and reproduced by permission of the *Canadian Journal of Biochemistry and Physiology.*

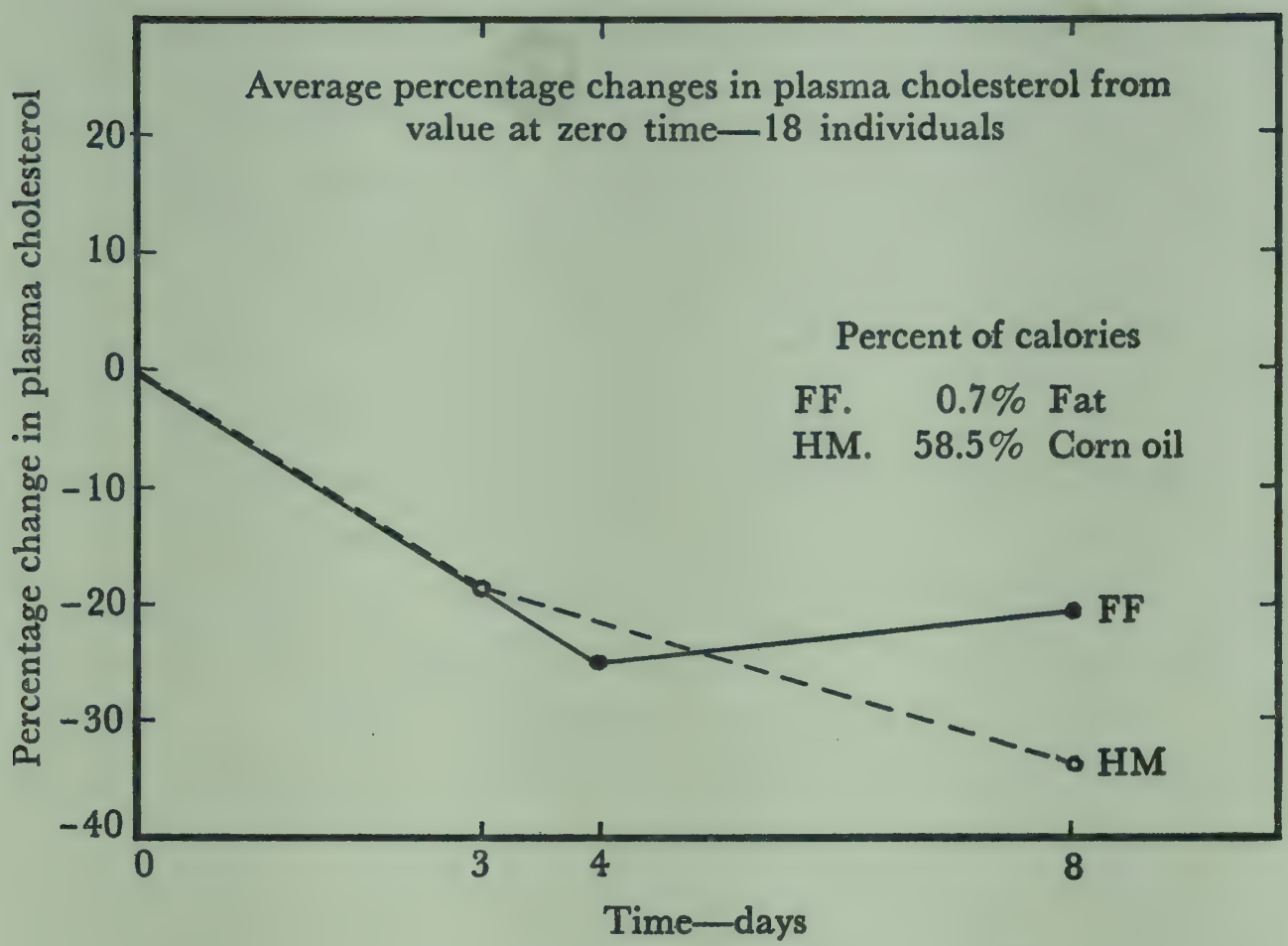
FIGURE 2



Averages of the individual percentage changes in plasma cholesterol for groups of medical students following an initial period of eight days on a fat-free diet and placement on diets varying in respect of the nature and level of the fat moiety.

Data reported by Beveridge *et al.*[27] and reproduced by permission of the *Canadian Journal of Biochemistry and Physiology*.

FIGURE 3



Comparison of the average of the individual percentage changes in plasma cholesterol in 18 medical students who ate a diet high in corn oil, HM, or a "fat-free" diet, FF, for a period of eight days.

Data reported by Beveridge *et al.*[27] and reproduced by permission of the *Canadian Journal of Biochemistry and Physiology.*

periods. The lowest serum lipid levels occurred during the intake of the corn oil formula and were lower than those obtained with olive oil, lard, or coconut oil formulas. Corn oil at 70 per cent caloric level in one case had a more pronounced effect than at a 10 per cent level. Furthermore, the serum cholesterol levels were not adversely affected when up to 4 grams of cholesterol per day were added to the corn oil formula.

During a four-month metabolic ward study of obese patients, Ahrens *et al.*[8] determined the effects on serum lipids of replacing animal fats isocalorically with vegetable fats. In these diets, fat supplied 45 to 52 per cent of the total calories. During the acclimatization and control periods, 93 per cent of the dietary fat was of animal origin, such as butter, cream and egg yolk, whereas during the test period over 99 per cent of the dietary fat was of vegetable origin, consisting primarily of corn oil and milk-free oleomargarine. Results of serum lipid analyses showed that (a) both free and total cholesterol levels decreased when vegetable oil replaced animal fat, (b) cholesterol levels decreased proportionately more than did phosphatide levels, and (c) neutral fat levels were not affected.

Malmros and Wigand[161] have come to the conclusion that the replacement of animal fats in the diet with vegetable fats is a promising means of treating hypercholesterolemia. In their experiments, the preferred vegetable fat was corn oil in the forms of an artificial milk, a cheese-like product, and a frozen dessert. As a result of tests on patients having normal serum cholesterol levels or having different types of hypercholesterolemia, Malmros and Wigand concluded the vegetable fat diet consistently produced a distinct fall in the serum cholesterol values, even in cases of hypercholesterolemia of the essential familial type which do not respond very well to other therapy.

Effects of Diet on Tissue Lipid Compositions

In a limited series of tests, vegetable oils of several types were found to differ in effectiveness. The favorable results obtained with corn oil were tentatively ascribed to the abundance of essential fatty acids in this oil.

By comparing, in short term experiments, the effects on human serum cholesterol levels of feeding diets containing various vegetable, fish and animal fats, Bronte-Stewart *et al.*[36] found that changes in the serum cholesterol levels coincided with changes in the intake of fat, independently of alterations in the protein, calorie, or vitamin intake. In quantitatively equivalent amounts, animal fats in the form of butter, beef drippings, beef muscle, and eggs caused a rise in serum cholesterol levels, whereas marine animal oils caused a drop either when fed alone after a fat-free diet or with eggs. Vegetable oils did not raise the serum cholesterol levels. The activity was associated with the highly unsaturated fatty acid fractions from pilchard oil and sunflower seed oil.

Hardinge and Stare[119] have also observed that vegetarians tend to have low serum cholesterol concentrations despite a free intake of vegetable fat. These workers, therefore, suggest that cholesterol levels may be more closely correlated to the intake of animal fat than that of total fat.

Similar effects of the substitution of vegetable oils for animal fats in the diet have been observed in schizophrenics[16] and in a variety of diseased states.[56,95,139,143,145,146] Thus, there seems little reason to doubt that blood cholesterol levels are profoundly affected by the nature of the dietary fat. Unsaturated vegetable oils, in particular, hold promise as effective agents for decreasing cholesterol concentrations.

Effect on Liver Lipids

For obvious reasons, the effects of dietary fat on liver lipids

have usually been studied in experimental animals. Whether these data are applicable in all details to human beings remains to be determined.

The liver plays an important role in the intermediary metabolism of lipids, modifying them for use in other tissues. As a consequence, the liver is a temporary storage organ for fats, and its lipid composition may fluctuate markedly. Fatty acids of liver lipids interchange rapidly with those in the blood.[63] Significantly, liver lipids are less saturated than those of adipose tissue, and thus indicate the important role of the unsaturated fatty acids in the intermediary metabolism of fats.

Although most of the responses of liver lipids to dietary fats are transient, permanent changes in quantity and composition may occur. Many of these may result from deficiencies of lipotropic agents or hormone imbalances and, hence, are not part of the present discussion.

The nature of the dietary fat may, however, have an important bearing on the metabolism of cholesterol and its accumulation in the liver. Lard as the sole dietary source of fat led to higher liver cholesterol values in rats than did cottonseed oil.[7,171] In addition, the total amount of cholesterol in the carcass was greater in the lard-fed animals. When rats were fed low-protein diets containing 20 per cent fat, the amount of liver fat was high on butter or lard rations, and low on corn oil or margarine.[22]

These observations are in accord with the known differences between these fats in the nature and proportion of the unsaturated fatty acids (Table I-A). The data also support the hypothesis (page 33) that cholesterol esters of the unsaturated fatty acids are more labile than the saturated esters, and thus do not accumulate so readily in the tissues.

IV

Essential Fatty Acids

UNTIL ABOUT THIRTY YEARS AGO, most biochemists believed that animals would grow satisfactorily and remain healthy without eating fats. The first indications that such a belief was false were noticed when mice on a completely lipid-free diet lost weight and became quite susceptible to infections.[132] Also, when fat was totally excluded from a diet containing adequate amounts of all known vitamins, that diet failed to support the growth or well-being of rats.[42,78,163]

Burr and Burr[42,43] first described the fat-deficiency symptoms in detail, emphasizing the poor growth, caudal necrosis, scaliness of feet and skin, urinary tract and kidney damage, increased water consumption not accompanied by increased urine volume, and pregnancy difficulties. In small quantities, butter and coconut oil had no curative effect, olive oil was intermediate, and corn and linseed oils were particularly effective in curing the deficiency symptoms. In other words, the curative power appeared to depend on the proportion of linoleic and possibly other highly unsaturated fatty acids in the fat. These, then, became known as the *essential fatty acids*.

Although Burr and Burr emphasized that great care must

be exercised in drawing conclusions concerning human nutrition from results with rats, they pointed out[43] that the fat consumption of humans is often exceedingly low. Furthermore, dietary fats may be deficient in the acids more unsaturated than oleic. In consequence diets high in carbohydrate and protein may be contributing factors to poor health.

Although acute fat-deficiency symptoms have rarely been observed in humans, there is a strong possibility that chronic deficiencies of the essential fatty acids may be widespread in spite of the relatively high proportion of fat in the average American diet.[112,170,207] As more investigators have learned to recognize the symptoms, there has arisen an increasing awareness of the similarities between certain human disorders and the essential fatty acid deficiency syndrome which has been observed in rats and also in mice,[50,61,194,235] guinea pigs,[185,186] hamsters,[55,203] chickens, [30,187] and dogs.[116,239,240]

Nature and Occurrence

The first experiments indicated that the fat-deficiency syndrome resulted from a lack of unsaturated fat and was promptly cured by the administration of esters of linoleic acid.[43] Further studies[39,45,130,131,227] proved conclusively that three highly unsaturated fatty acids, namely, *linoleic* (VII), *linolenic* (VIII) and *arachidonic* (IX), have essential fatty acid activity. Saturated, mono-unsaturated, and very highly unsaturated fatty acids have little, if any, activity.[39,60,65,120,223a,227]

The three essential fatty acids are not equally potent, however.[39,130,131] For example, linoleic acid is effective in promoting growth, curing dermatitis and other fat-deficiency symptoms. Linolenic acid has a growth-promoting action but is unable to prevent or cure the skin abnormalities.

$$CH_3(CH_2)_4CH=CHCH_2CH=CH(CH_2)_7COOH$$

VII

$$CH_3CH_2CH=CHCH_2CH=CHCH_2CH=CH(CH_2)_7COOH$$

VIII

$$CH_3(CH_2)_4CH=CHCH_2CH=CHCH_2CH=CHCH_2CH=CH(CH_2)_3COOH$$

IX

As has now been demonstrated conclusively,[18,23,165,189,216,217,236,237] linoleic acid is not readily synthesized in animals but can be used in the formation of arachidonic acid. By contrast linolenic cannot be converted to either linoleic or arachidonic. Therefore, linoleic acid appears to be the primary factor and *must be* supplied in the diet. Analyses of human blood lipids have also shown that there are significant changes in the proportions of the unsaturated fatty acids when the intake of linoleic acid is limited,[38,108,117,118,238,242] and that the increase in trienoic acid level and decreases in dienoic and tetraenoic are comparable to those in fat-deficient dogs.[237a]

Because two double bonds are present in the molecule, linoleic acid exists in several different isomeric forms. Not unexpectedly, it has been found[120,126,178] that the naturally occurring isomer has the greatest potency. The unnatural isomers have little or no essential fatty acid activity, although they may be utilized for energy.

This question of the activity of the isomeric acids has an important bearing on the nutritive value of margarines, shortenings and other products made by the hydrogenation of vegetable oils, such as cottonseed or soybean oil. The digestibility and utilization of these products for energy have been proved[69,71,166] to be equivalent to those of other fats having the same melting point. However, the hydrogenation processes

reduce the content of essential fatty acids, make the oil more saturated and, consequently, more like animal fats. It is generally agreed that isomers not found in natural fats are produced during this process,[13,160,166,212] and that the method of hydrogenation determines how much linoleic acid remains in the shortening. A completely saturated fat, such as hydrogenated coconut oil, was found[166] to be somewhat deleterious because it apparently increased the animal's requirements for the essential fatty acids.

The relative amounts of linoleic, linolenic and arachidonic acids in various vegetable oils, and animal and hydrogenated fat are summarized in Table I-A (page 8). As a general rule, vegetable oils which have been subjected only to refining processes are richer sources of the essential fatty acids than are hydrogenated shortenings and animal fats.

Effect on Growth

One of the first indications of the essential role of dietary fat was the observation that the rate of growth of weanling rats on a fat-free diet was very much below normal. Furthermore, these animals matured slowly. The abundant evidence supporting these first observations has led to the conclusion that the *essential fatty acids have a key position in the formation and development of new cells,*[61] but the specific function is still uncertain.

The early disagreements concerning the nature of the essential fatty acids bear testimony to the complexity of the growth effect. Much work remains to be done but the accumulating data indicate that the growth response to fats is partly determined by the relative proportions of the different fatty acids, both unsaturated and saturated, and, by the total quantity

of lipids in the diet. Thus, for example, in guinea pigs a diet containing hydrogenated lard permitted better growth than a fat-free diet but was very much inferior in this respect to a diet containing corn oil.[186]

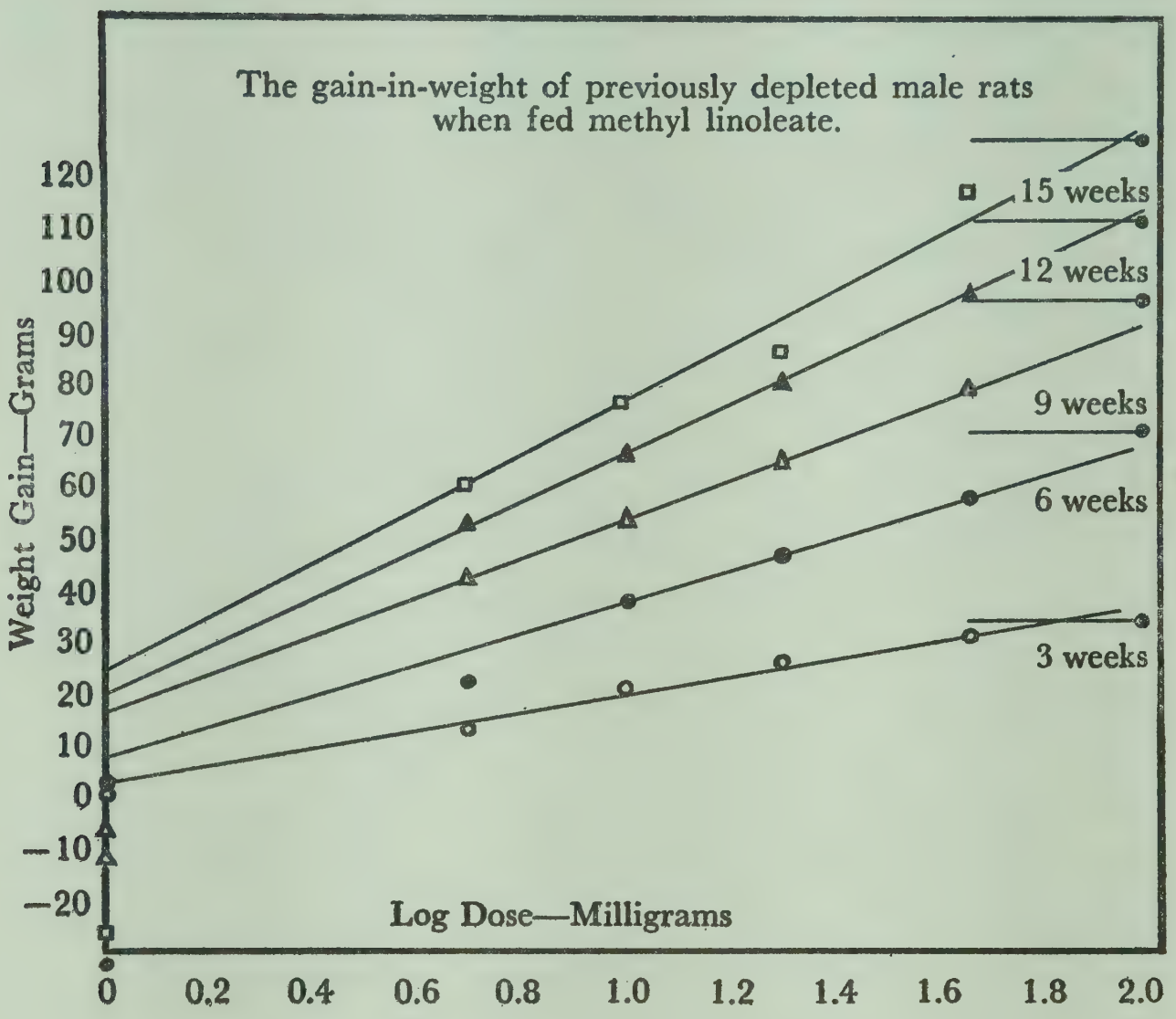
Figure 4 presents a summary of typical data showing that when methyl linoleate is added to a fat-free diet, the rates of growth of fat-deficient male rats are proportional to the dosage. This finding is the basis of various bioassay procedures for the determination of essential fatty acids in fats and oils.[69,130,131,166,223a]

At minimal levels in fat-free diets, linolenate was found to be less active than linoleate when these were fed separately.[39,65,120] However, when fed together linoleate apparently "sparked" the linolenate so that the activity of the combination was greater than would be predicted from the individual activities.[103,178]

Even more important to the present discussion is the effect of dietary fat itself. Rats receiving adequate amounts of linoleate grew even more rapidly when cottonseed oil was also included in the diet.[70,102,103] Similarly, in diets containing sufficient corn oil to supply essential fatty acids, the addition of lard[89] or hydrogenated cottonseed oil[84] increased the growth rate.

This beneficial effect of added fat has been observed in animals which were depleted by fat-free diets but not in those depleted by diets containing saturated fats, such as hydrogenated peanut oil.[6] Furthermore, a completely saturated fat, such as hydrogenated coconut oil[67] or hydrogenated peanut oil,[4,5] when added to diets containing marginal amounts of essential fatty acids was found to have a suppressing effect on growth. *Such observations have led to the hypothesis that the requirement for essential fatty acids is increased when the diet contains large amounts of saturated or unnatural isomeric fats.* Supports for this hypothesis are found in studies showing that

FIGURE 4



The gain-in-weight of previously depleted male rats fed methyl linoleate for 3, 6, 9, 12 and 15 weeks. Doses of methyl linoleate were 5, 10, 20 and 50 mg. daily.

Data reported by Greenberg *et al.*[103] and reproduced by permission of the *Journal of Nutrition.*

diets containing hydrogenated peanut oil produced fat-deficiency symptoms equivalent to those of fat-free diets,[1,2,3,4] and hydrogenated coconut oil accelerated the onset of fat-deficiency symptoms.[67]

Infants, when permitted to regulate their food intake, apparently respond to the availability of linoleic acid in the formula.[111a] Thus, while growing at the same rate, nursing infants required fewer calories than did babies receiving typical evaporated milk formulas. This effect was related to the higher linoleic acid content of human milk as compared to cow's milk, rather than to total fat.

Effect on Pregnancy and Lactation

Closely related to the growth-promoting activity of the essential fatty acids is their effect on pregnancy and lactation. Some of the earliest work with fat-free diets demonstrated that reproductive failure always resulted when rats were raised on such diets.[39,79,80,81,179] The delayed sexual maturity of the animals[66] and the uterine and placental bleeding were prevented by addition of essential fatty acids to the diet.[179] There were indications[72] that fat might not be required for conception, development of fetuses or parturition, but that essential fatty acids were required for the survival of the young during the first three days postpartum. Corn oil was found[157] to stimulate lactation and resulted in more rapid gains in the young before weaning than did hydrogenated corn and coconut oils.

Kummerow *et al.*,[152] after a comparison of fat-free diets with diets containing 5 per cent of hydrogenated fat or 5 per cent of corn oil, concluded that a dietary source of unsaturated fat, such as corn oil, was necessary for normal reproduction and lactation of rats. In these experiments, the commercially

available hydrogenated fat was not sufficiently unsaturated to meet requirements of the rats for normal lactation, and the young died soon after birth. When the diet contained inadequate amounts of unsaturated fats, the difficulty noted during parturition seemed to result from poor muscle tone of the uterine wall, possibly involving a fundamental change in the mixed fatty acid composition of the lipoproteins in the muscle fibers.

Measured in terms of ability to satisfy demands of pregnancy and lactation, the biopotency of linoleate appears to be greater than that of linolenate at all levels. However, just as in the case of growth activity, a synergism has been observed when both linoleate and linolenate were fed.[73]

Effects on the Skin

The effects of essential fatty acids on the skin are no less striking than their effects on growth. From the beginning, the curing of caudal necrosis, dermatitis and other epidermal abnormalities has been a criterion for estimating the essential fatty acid activity of various fats and oils.[41,43,130,131]

In the early experiments, workers in different laboratories frequently disagreed about the effects of a given diet on the severity of dermal symptoms. Eventually, the discrepancies were shown to arise from two secondary circumstances: unrecognized deficiencies of certain vitamins (a point which is discussed in detail on page 39), and the relative humidities of the animal rooms. Burr and Burr[43] observed initially that the fat-deficient animals consumed large quantities of water without a corresponding increase in urine volume or gain in weight. Subsequently, this effect was proved[206] to result from increased losses of water through the skin. In consequence, the severity

of dermal effects varies inversely with the humidity, being most intense at low relative humidities,[1,3,39] and an increased consumption of water is one of the earliest indications of essential fatty acid deficiency.[5,43,61,223a]

Only linoleic and arachidonic acid esters are able to cure the skin abnormalities.[39,41,63,120] Linolenate has little, if any, effect except in the presence of linoleate.[103] The curative and preventive powers of oils and fats are therefore proportional to their contents of linoleic and arachidonic acids. The activity of corn oil in this respect has been amply demonstrated in rats,[19,41,43,44] mice,[61] chicks,[30] guinea pigs,[185] and humans (see below).

Incidental to other studies, workers have often noted that fat-deficient animals are less resistant to infections than normal.[61,237] A particularly suggestive observation along these lines was made by Decker *et al.*[61] who reported that when blood samples were taken from fat-deficient mature mice, the skin punctures and wounds healed more slowly than in control animals which were allowed ready access to corn oil in addition to the fat-free diet. A control animal which was injured accidentally increased its consumption of corn oil two to threefold during the healing period.

So dramatic is the effect of essential fatty acids on the skin of a weanling animal that their possibilities in the treatment of human eczema soon aroused the interest of pediatricians. In 1933, Hansen[109] first reported that eczema in 11 infants was substantially reduced by the administration of corn or linseed oil. Furthermore, he found that the levels of unsaturated fatty acids in the blood of these eczematous infants were below normal, and rose during treatment with the oil.

In a more extensive study,[57] Cornbleet used corn oil in the treatment of 87 patients over five years of age including

many who had suffered from eczema since infancy. Up to 4 tablespoons of corn oil daily eventually brought the eczema under control in most cases. The capriciousness of the eczema and the long time (12 to 18 months) needed to achieve permanent results were particularly emphasized. In short-term experiments, relapses were frequent and often severe.

The correlation of low serum levels of unsaturated fatty acids in patients having eczema with the responsiveness to treatment with corn oil, or other sources of essential fatty acids, has been repeatedly demonstrated.[37,82,85,110,111,121,219,221] It has also been noted that the milk of mothers nursing eczematous infants apparently contained somewhat smaller proportions of highly unsaturated fatty acids than did the milk of mothers with noneczematous infants.[114] In addition infants maintained on breast milk were thought to be less apt to have eczema[114, 120,208] or skin eruptions than those receiving cow's milk, which is known to have a lower linoleic acid content than human milk. As would be expected, adults and adolescents were less responsive than infants to treatment with unsaturated fats.[120]

In this connection, it is of interest to note that in patients suffering from cholecystitis and cholelithiasis who were maintained on a fat-free diet (less than one per cent of the daily caloric intake as hidden fat) for one year or longer, there was a gradual decrease in circulating blood levels of unsaturated fatty acids, accompanied by the development of dry skin with various degrees of desquamation.[196] A similar effect has occasionally been observed in patients maintained for long periods on the Kempner rice diet.[234]

Microscopic examinations have revealed important changes in the skin caused by diets deficient in essential fatty acids. The plugging of the follicular openings with dense, compact layers of keratin which has been observed in rats on essential

fatty acid-deficient diets[183] was thought to be histologically similar to follicular hyperkeratosis in man.[184,206] In mice and rats, the most notable changes were in the differentiation of the epidermis and the enlargement of the sebaceous glands[48] accompanied by increased sensitivity to injuries and increased permeability to water.[206] In dogs, a low-fat diet resulted in significant decreases in the proportion of the essential fatty acids in the skin[120,241] and marked changes in its histological structure.[113,115,120]

So complex a condition as eczema can hardly be expected to respond to any one treatment. Experience to date, however, leads to the conclusion that *when serum levels of the essential fatty acids are low, the dietary use of unsaturated vegetable oils, such as corn oil, may at least increase the effectiveness of other treatments.*

Relationship to Cholesterol

The fact that a high proportion of the cholesterol in blood serum exists as the esters of the unsaturated fatty acids has long been known.[32,33,63] An attractive hypothesis is that these esters are more easily metabolized and more "soluble" in the blood than are the esters of the saturated acids. Although much additional research is needed to elucidate the specific role played by the essential fatty acids in the metabolism of cholesterol, there is now little doubt that there is an intimate connection. A particularly interesting possibility is suggested by results of experiments with rat liver homogenates which showed[245] that linoleic acid markedly inhibited cholesterol synthesis.

In 1954, Alfin-Slater *et al.*[11] reported studies on the distribution of cholesterol in the plasma and tissues of essential fatty acid-deficient rats. The data showed that, although the levels

of cholesterol in the plasma were lower than normal, the levels in the liver and adrenal glands were high as compared to those in animals receiving 12.5 per cent of cottonseed oil. Because the increased level in the liver of fat-deficient animals was almost entirely confined to the cholesterol ester fraction, the suggestion was made that these changes indicate a failure of cholesterol esters containing other than polyunsaturated acids to be available for proper metabolism. Subsequently, it was shown[67] that hydrogenated coconut oil as the sole fat in the diet caused a more rapid appearance of these deficiency changes than did a fat-free diet. Linoleate supplements quickly brought cholesterol ester levels to normal. In addition, conditions which promote hypercholesterolemia, such as diabetes or cholesterol feeding, have been shown to accelerate the onset of essential fatty acid deficiency in rats[175] and in rabbits.[176]

That similar effects may also be observed in humans is evident from the previous discussion of the relationship between unsaturation of dietary fats and serum cholesterol levels (page 15). The relationship was clearly demonstrated when humans were given a synthetic triglyceride as the only source of fat.[142,145a] At an intake which provided about 2 grams of linoleic acid daily, there was a decrease in the plasma cholesterol levels. However, hydrogenated coconut oil (which contains no essential fatty acids) caused a progressive rise in the plasma cholesterol levels. Furthermore, Bronte-Stewart *et al.*[36] have reported that the factor which depressed serum cholesterol levels occurs in the highly unsaturated fatty acid fraction from seed and fish oils. The saturated fatty acid fraction, on the other hand, caused an elevation in serum cholesterol levels.

Thus the working hypothesis is that for humans as well as animals an adequate intake of essential fatty acids is needed for the maintenance of normal cholesterol levels.

Effects on Internal Organs

Spectrophotometric studies of tissue lipids in humans[108,117,238,242] and animals[18,127,237,241] have shown that fat-deficient diets may cause appreciable changes in the proportions of the unsaturated fatty acids. Accompanying these changes in composition may be significant microscopic changes in the cells.

In experimental animals one of the signs of severe essential fatty acid-deficiency is hematuria.[3,120] Histological studies[5,34,39,86] have shown considerable calcification of renal tubules and necrotic areas of the renal medula.

As a primary organ in the metabolism of lipids the liver responds quickly to alterations in dietary fat. One instance is the accumulation of cholesterol previously discussed. Although an accumulation of lipids in the livers of fat-deficient animals is frequently observed, this effect cannot be ascribed entirely to a lack of essential fatty acids since various vitamins and lipotropic agents (page 39) may also be involved. Arachidonic acid appears to be a particularly important factor in maintaining optimum fat turnover.[168,190,209]

Studies have also shown that when rats received 5 per cent corn oil in their diets, phosphorus was incorporated in the liver phosphatides at a normal rate, but in fat-deficient animals the rate was very low.[149] When the fat content of the diet has been low, important changes in the nature and distribution of the unsaturated fatty acids in the liver cytoplasmic particles have been observed.[147,148,168] *These results indicate that fundamental changes in the liver resulting from insufficient supplies of essential fatty acids may appear long before external symptoms are evident.*

Similar changes in the subcellular particles in the livers have been observed when rats were raised on commercial diets but

not when the diets contained high levels of unsaturated fats. These findings have led to the suggestion that although a diet may appear to be adequate for growth and reproduction, it may not meet the nutritive requirements of old animals.[147]

Profound effects of fat-deficiency on many internal organs have been revealed in detailed studies of male and female rats.[172,173] Autopsy showed the expected relatively heavy liver, heart and kidneys, with intertubular accumulation of blood in the kidneys and fatty accumulations in the hepatic veins. The effects on the endocrine system were particularly noted: small thyroids in both sexes, heavy adrenals in the males but possibly smaller in the females, and more or less genital degeneration in the males and irregular estrous cycles in the females. Histological examinations indicated[159] that essential fatty acid-deficiency caused underdevelopment of the uterine mucosa and corpora lutea with the result that embryos were resorbed or retained beyond the normal gestation period. In the essential fatty acid-deficient male rat[81] there was atrophy of the testes, degeneration of the tubular epithelium, absence of sperm, and the appearance of giant cells. The seminal vesicles were small and flaccid, and the prostate was atrophic. Essential fatty acid-deficiency has been associated with the accumulation of foamy phagocytic cells in the lungs of rats.[182]

Although the relationship between essential fatty acids and cholesterol with its possible implications in atherosclerosis has already been discussed (pages 15, 33), a direct effect of essential fatty acids on capillary resistance merits comment here. In studies with humans, Kramár and co-workers[150] noted that the capillary resistance of patients, especially those with allergic manifestations, was higher on a vegetable fat diet than on one in which the fat was exclusively of animal origin. This observation may be correlated with the finding that immature albino

rats fed fat-free or synthetic diets containing methyl stearate manifested pathologically low capillary resistance. The drop occurred simultaneously with the flattening of the weight curve but before the characteristic skin symptoms of fat-deficiency were evident. When the same basic diet contained 5 per cent corn oil, the capillary resistance remained normal. *Presumably, therefore, the essential fatty acids may also play a part in the maintenance of a healthy vascular system.*

Effect of Stress Conditions

It is generally conceded that requirements for essential nutrients can be tested most easily by subjecting animals to stress conditions. The feeding of large amounts of saturated fats or cholesterol represents a type of stress which increases the requirements for essential fatty acids and accelerates the onset of deficiencies (page 33).

A more usual type of stress is imposed by caloric restrictions. In experiments with rats, vegetable oil in the diet was found to reduce the catabolism of tissue protein when the diet was protein-free and caloric intake was strictly limited.[92] The protective effect was associated with the unsaturated acids in the fat and was ascribed to linoleic acid. This study also indicated that the need for essential fatty acids was increased under these conditions to levels appreciably above those ordinarily considered adequate.

A deranged lipid metabolism in diabetes has long been recognized. Most obvious is the increased incidence of atherosclerosis and ketosis. Young rats made diabetic by the injection of alloxan and maintained on a low-fat diet developed characteristic symptoms of essential fatty acid-deficiency in a month as compared to three months in the untreated animals.[175]

This increase in the requirement for essential fatty acids was comparable to that resulting from the feeding of cholesterol to the untreated animals. *These results suggest that the tendency to atherosclerosis may be influenced by the availability of the essential fatty acids.* Possible support for this hypothesis is the observation that the inclusion of vegetable fat in high-protein reducing diets for human diabetics was followed by a drop in serum cholesterol and phosphatide levels even in the absence of hypercholesterolemia.[144] Such dietary treatment may have a definite therapeutic value.[140]

The feeding of desiccated thyroid to rats accentuated the growth retardation and significantly reduced the survival time on fat-deficient diets.[77,101,104] These effects were counteracted by the administration of methyl linoleate or an unsaturated vegetable oil which, however, did not completely prevent the enlargement of heart and kidneys resulting from the action of the thyroid substance. Whether this effect was due to a direct action of the unsaturated fatty acids, or to their ability to stimulate production of necessary factors by intestinal bacteria, remains to be decided. These observations may have clinical significance, however, since such small doses of thyroid powder produced the harmful effects on fat-low diets.[104] In rats, the weight-reducing effect of desiccated thyroid was partially counteracted by the feeding of corn oil.[138]

The decreased resistance of fat-deficient animals to infections and the lower rate of wound healing have already been noted (pages 23, 31). A possibly parallel observation has been made in humans. Acute infections in children were found to be associated with low serum lipid levels[164,218,219] which returned to normal during convalescence. Artificially induced fever did not have this effect. In eczematous infants, acute infections were accompanied by a brief improvement in the

skin conditions followed by rapid, severe aggravation.[220,221] These changes in the skin were related to the changes in the degree of unsaturation in the serum fatty acids, which was lowest at the height of the infection.

A form of stress which is unique in modern times is x-irradiation. Decker *et al.*[61] first observed that corn oil increased the resistance of mice to radiation damage and ascribed the results to the action of the essential fatty acids. Dietary fat had no protective effect against x-irradiation injury after a single large dose but did reduce injury after repeated sublethal doses.[53] This protective effect has been correlated with the essential fatty acid content of the diet.[54,68] Furthermore, the minimum effective doses of essential fatty acids, or of unsaturated vegetable oils, were of the same order of magnitude as those required for growth and were greater for males than females.[51, 52,54] Linoleic acid appeared to be a protective factor; linolenic acid was without effect except when linoleic acid was also present.[52] The bone marrow of irradiated rabbits was found to contain significantly increased concentrations of linoleic and linolenic acids, and total fat.[24]

These results suggest that unsaturated fats have a protective action against radiation injury because of their ability to stimulate the growth of new tissue rather than because of any specific activity. The survival time has been correlated with increases in the less dense serum lipoprotein fractions.[99,122,123]

Relationship to Vitamins

Many of the disagreements regarding the roles of essential fatty acids may be ascribed to two facts. First, symptoms are difficult to detect in mature animals in which the requirements are not the same as in growing animals and may be met for

extended periods by the re-utilization of tissue lipids. Support for such a hypothesis is given by the tenacious retention of highly unsaturated fatty acids in the tissues even during prolonged maintenance of animals on fat-deficient diets.[32,63,120] Second, symptoms of fat-deficiencies are quite similar to those caused by certain vitamin deficiencies.

The following discussion considers some of the interrelationships of the essential fatty acids with the B-vitamins but does not include the fat-soluble vitamins. In the latter case, the effects are comparable to those of antioxidants and proöxidants, and therefore are believed to be nonspecific.

In the strictest definition of the term, essential fatty acids are lipotropic agents[98] because of their ability to aid in removal of excessive deposits of lipids from the liver, and because one secondary effect of the deficiency is an altered lipid metabolism in the liver (page 35). Not unexpectedly, therefore, Engel[76] in 1942 found that both pyridoxine and a source of essential fatty acids, such as corn oil, were necessary for optimum action of choline as a lipotropic agent in rats. However, the lipotropic action of inositol could be demonstrated only in the absence of unsaturated fat.[29]

The marked similarity of the dermatitis resulting from deficiencies of essential fatty acids and that from deficiencies of pyridoxine early attracted attention. In 1938, Birch[31] and Salmon[191] reported that an acrodynia-like dermatitis was cured by two factors: vitamin B_6 (pyridoxine) and the unsaturated fatty acids in vegetable oils. Shortly thereafter, linseed oil was shown[180] to be less effective than corn oil in reducing signs of pyridoxine-deficiency dermatitis. This effect was in line with the known differences in linoleic acid content of these two oils.

Subsequent studies proved that the curative power of linoleic acid was enhanced by vitamin B_6.[106,195] Furthermore, corn

oil and pyridoxine, together, readily cured a biotin-deficiency dermatitis caused by feeding of dried egg whites to rats.[158] Finally, it was found that although the acrodynia did not appear in rats receiving adequate amounts of corn oil and pantothenic acid, sustained growth resulted only when pyridoxine was also present.[181] Although the feeding of corn oil in a pyridoxine-free diet could not prevent the appearance of acrodynia, it did lessen the severity of the external symptoms.[20] Histological studies[184,206] showed that skin changes in essential fatty acid-deficiency were significantly different from those caused by a simple pyridoxine deficiency.

Recent work has elucidated part of the role of pyridoxine in essential fatty acid metabolism[49,60,201,205] by showing that pyridoxine has a still undefined function in the enzyme systems which convert linoleic to arachidonic acid,[210,225,226,244] and possibly convert linolenic to more unsaturated acids.

Results of limited clinical studies have led to suggestions that dermatitis,[232] atherosclerosis[198,199,207] and bronchial asthma[204] in humans may be manifestations of a deficiency which may be most effectively treated by the synergistic combination of essential fatty acids and pyridoxine.

V

Human Requirements

GRANTED THAT human beings prefer to have fats in their diets and will probably persist in eating them, what guides do we have to the selection of the best fats and the establishment of optimum levels?

The 1948 report of the Food and Nutrition Board of the National Research Council[87] made the following suggestion: "There is available little information concerning the human requirement for fat. Fat allowances must be based at present more on food habits than on physiological requirements. While a requirement for certain unsaturated fatty acids (the linoleic and arachidonic acids of natural fats) has been amply demonstrated with experimental animals, the human need for these fatty acids is not known. In spite of the paucity of information on this subject, there are several factors which make it desirable (1) that fats be included in the diet to the extent of at least *20 to 25 per cent* of the total calories and (2) that the fat intake include essential unsaturated fatty acids to the extent of *at least 1 per cent* of the total calories. At higher levels of energy expenditure, *e.g.*, for a very active person consuming 4500 calories and for children and for adoles-

cent persons, it is desirable that *30 to 35 per cent* of the total calories be derived from fat. Since foodstuffs such as meat, cheese, nuts, etc., contribute fat to the diet, it is necessary to use separated or 'visible' fat such as butter, oleomargarine, lard, or shortenings to supply only one-third to one-half the amounts indicated."

To a considerable extent the "hidden" fats are contained in animal products which are also excellent sources of protein. For optimum nutrition, these must remain in the diet. But experience gained since 1948 has led many authorities to believe that *the "visible" fats should preferably be vegetable oils and that the consumption of animal fats and hydrogenated shortenings should be limited*. For example, Brock and co-workers[35] point out that the quality of dietary fat may be more important than quantity and that although the story is still incomplete, fats and oils rich in polyunsaturated fatty acids may be preferable to those which are rich in saturated fatty acids.

The bases for such recommendations are: (1) The ability of the human body to synthesize essential fatty acids is apparently so limited that most, if not all, of the linoleic acid must be supplied in the food. (2) Vegetable oils contain more of the essential fatty acids than do animal fats. (3) Certain serious medical problems bear some resemblance to syndromes in animals raised on diets deficient in these acids.

Atherosclerosis is characterized by the accumulation of lipids, particularly cholesterol, in the arterial walls. As Keys has stated:[135] "Many factors are probably involved in the atherosclerotic development and in the clinical appearance of coronary heart disease, but there is no longer any doubt that one central item is the concentration, over time, of cholesterol and related lipids and lipoproteins in the blood serum. No

other etiological influence of comparable importance is as yet identified . . . . . ." Similarly, Gutman[107] has observed that the basic cause appears to be a *metabolic defect* involving the biosynthesis, transport and catabolism or excretion of certain lipids, notably the lipoproteins containing cholesterol.

As is apparent from data reviewed in this monograph, *extensive studies with animals have proved that the metabolisms of linoleic acid and cholesterol are closely related, that linoleic acid has lipotropic activity, and that excessive consumption of saturated fats or cholesterol increases the need for essential fatty acids.* In line with these data are the results of clinical studies in which human serum cholesterol levels were significantly reduced when corn oil was the sole fat in the diet.

The importance of both the nature and the quantity of dietary fat has become particularly apparent as a result of recent ethnologic studies. The accumulated data have led competent authorities[169] to state that: "The possibility that high fat intakes are undesirable has been emphasized by studies upon the incidence of arteriosclerosis in various countries compared to their usual fat intake. As far as the present data go, countries with low fat intakes also appear to have low incidence of heart disease and the blood cholesterol levels of the population are lower. The interpretation of such data as cause and effect may well be hazardous since other correlations might also be found. Nevertheless, this indication deserves careful study in view of the large and increasing proportion of fat in the American diet." Not to be overlooked with respect to these observations is the fact that in low-fat areas the fat is chiefly of vegetable, rather than of animal, origin. As has been observed in Guatemala,[108] although the diets of the natives contained less than 4 per cent of fat, this was derived chiefly from corn and appeared to be adequate, since blood levels of all

polyunsaturated fatty acids were normal or above. Such data have led Katz *et al.*[133a] to postulate that the critical factor may not be the fat intake, alone, but instead may be the ratio of caloric intake to the level of essential nutrients, including unsaturated fatty acids.

The infantile eczemas discussed in an earlier chapter were clearly improved by increased consumption of the essential fatty acids. Only much painstaking research can prove conclusively whether these acids are required in humans, as they are in animals, for the maintenance of healthy liver, kidneys and endocrine organs. There are many intriguing possibilities for intensive clinical study in the observations that male animals require more of the essential fatty acids than do females, that there is a greater and earlier incidence of atherosclerosis in males than in females, that these acids increase resistance to many types of stress, and that excessive consumption of saturated fats and cholesterol accelerate the appearance of fat-deficiency symptoms.

If human requirements can be estimated from those of experimental animals, then we should eat enough unsaturated fat to provide no less than 3 grams of linoleic acid each day.[129] Evidence is increasing that the optimal level of essential fatty acids should be in the range of 6 to 19 grams for a daily intake of 2500 calories.[170] In view of this lack of specific information, Kinsell[141] advocates that: "Until further knowledge is available, one might conclude that avoiding obesity, and ingesting a nutritionally adequate diet, containing more than 50 grams of unsaturated fat, would be advisable for the individual over the age of 35."

Most certainly we can agree with Scheer and coworkers[193] that fats take an active part in a variety of fundamental physiological processes. Fat can no longer be regarded merely as the

inert storage material of the older biochemistry. Lipids are now known to be irreplaceable components of the metabolic machinery which may be profoundly affected by the availability of certain types of fat in the diet.

Summary

NUTRITION is unquestionably one of the most important factors influencing human health, well-being and longevity. The dramatic advances which followed the discovery of vitamins and other accessory food factors and their use as dietary supplements tended temporarily to draw attention away from the major classes of foodstuffs, the fats, proteins and carbohydrates.

Today, it is becoming increasingly apparent that fats have highly important nutritional functions beyond serving as concentrated sources of energy. From data gathered in many parts of the world, investigators are coming to the conclusions that both the quality and the quantity of dietary fat markedly influence the over-all health pattern of the populations and that, particularly in the more prosperous areas, diets probably deviate considerably from the optimum in fat content. The opinion is becoming more and more widespread that unsaturated vegetable oils, such as MAZOLA brand corn oil, possess distinct nutritional advantages. For example, the fact that diets containing corn oil result in lower serum cholesterol levels than do those containing more highly saturated fats has led to the hope that the incidence and course of atherosclerosis may be

influenced favorably, in part at least, by dietary means.

This favorable effect of corn oil has been attributed to the presence of two different types of compounds capable of lowering serum cholesterol levels, namely sitosterols and essential fatty acids. In addition to a relationship to cholesterol metabolism, the essential fatty acids also appear to have important functions in the development of new cells and the maintenance of healthy body tissues, particularly the skin, liver and kidneys. Requirements for the essential fatty acids seem to be increased when food yields large amounts of saturated or isomeric fatty acids, as may be the case in American diets rich in animal and hydrogenated vegetable fats.

There is, at present sharp disagreement about the quantity of dietary fat which is best from the viewpoint of growth, longevity, and well-being of the individual at all stages of his life span. However, no authority questions that, for optimum nutrition, the diet must include fat and that the balance between saturated and unsaturated fats, as well as the total quantity, merits careful consideration.

Mazola® Corn Oil

MAZOLA is golden oil from corn, which has been carefully packaged to assure purity, palatability and uniformity, and is readily available at grocery stores in pint and quart bottles and gallon cans.

One hundred grams of MAZOLA corn oil will yield:
53 grams of linoleic acid
12 grams of saturated fatty acids
28 grams of oleic acid
1.5 grams of sitosterols
No cholesterol

Because MAZOLA corn oil is a liquid it is more easily handled than are animal or hydrogenated shortenings, and solid cooking fats. More important from the nutritional point of view, this corn oil has *not* been hydrogenated and is a particularly rich natural source of linoleic acid.

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Abbreviations for names of journals follow the usage of *Chemical Abstracts.*

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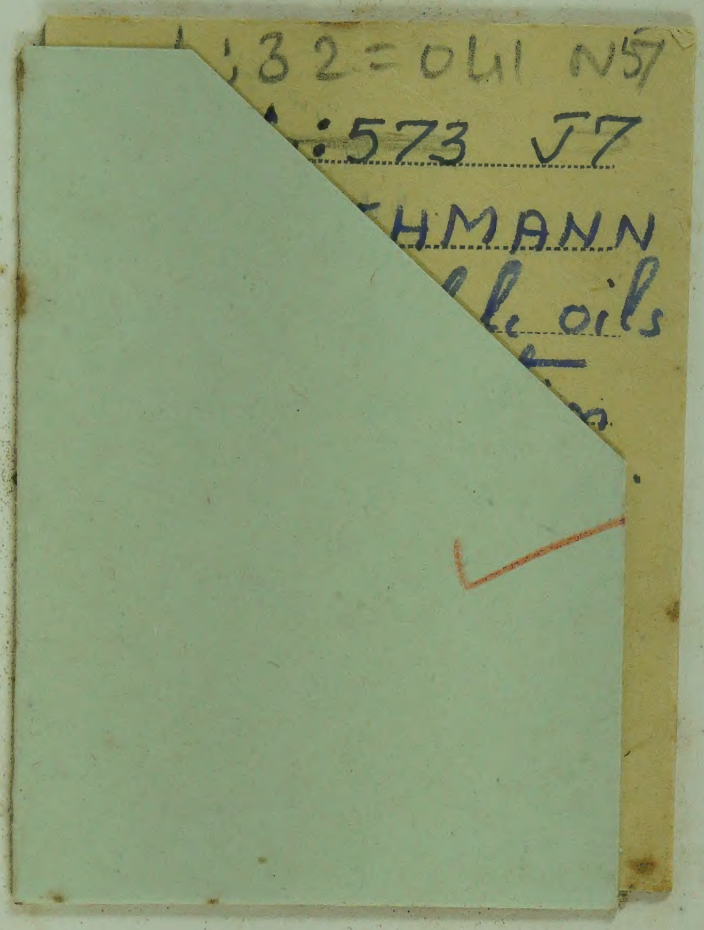
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